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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,333	07/17/2003	John C. Voyta	9550-016-27	8652

23552 7590 06/26/2006

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EXAMINER	
FOSTER, CHRISTINE E	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 06/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/620,333	VOYTA ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-45* is/are pending in the application.

4a) Of the above claim(s) *34-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-33 and 39-45* is/are rejected.

7)☒ Claim(s) *1,6,7,9,11,27,29,30,40 and 44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/28/03, 3/15/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-33 and 39-45, drawn to a method of detecting chemiluminescent emissions on a solid support, classified in class 435, subclass 6.

II. Claims 34-38, drawn to a composition comprising first and second chemiluminescent substrates, classified in class 549, subclass 200.

It is noted that claims 32-33 recite a "composition of Claim 1", yet claim 1 is drawn to a method and not to a composition. For the purposes of examination claims 32-33 were assumed to be directed to methods according to claim 1.

The inventions are distinct, each from the other because of the following reasons:

2. Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case the composition of Group II may be used by a process other than the method of Group I, for example, in a homogeneous detection method carried out in solution rather than on a solid support.

These inventions are distinct for the reasons given above, have acquired a separate status in the art because of their recognized divergent subject matter and as shown by their different classification. Moreover, the searches required for one group are not required for the others. In addition to the classification-based search of the patent literature, text searches of the non-patent

literature would also be non-coextensive due to the different limitations recited in each group. Therefore, restriction for examination purposes as indicated is proper.

Election of Species

3. This application contains claims directed to the following patentably distinct species:

   a. Type of target molecule (elect one of the following):

      i. Nucleic acid

      ii. Protein or polypeptide

   b. Type of probe molecule (elect one of the following):

      i. Protein or Polypeptide

      ii. Aptamer

      iii. Antibody

      iv. Nucleic acid

The species are independent or distinct because proteins/polypeptides and nucleic acids are chemically, structurally, and functionally different molecules with different properties and reactivities. Furthermore, although antibodies are types of proteins, they possess specific functional and structural characteristics in that they are capable of specifically binding to an antigen. Aptamers are also distinct in that they are RNA molecules with additional functionality, i.e. the capability of specifically binding to target molecules. Different searches of the patent and non-patent literature would be required in order to search all types of probe and target molecules. As such, it would be burdensome to search these Species together.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species (for both (a) and (b) above) for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1-9, 11-13, 18, 23-41, and 44-45 are generic. Claims 10, 14-17, 19-22, and 42-43 are subject to species election.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

2. During a telephone conversation with Steven Kelber on March 9, 2006 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-33 and 39-45 and the species of **nucleic acid** as the type of target molecule and probe molecule. Affirmation of this election must be made by applicant in replying to this Office action.

4. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

Applicant's Information Disclosure Statements filed 8/28/03 and 3/15/05 have been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached forms PTO-1449.

Priority

5. The first paragraph of the specification identifies the instant application as being "related" to copending applications 10/046,730 and 10/462,742, and to application 10/050,188 (now US 6,905,826). It is unclear whether Applicant intends to claim priority under 35 USC 120 to these applications by this reference.

If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 120, a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be included in the first sentence(s) of the specification following the title or in an application data sheet. **For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications**.

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the

date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Specification

6. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

7. Claims 39-40 refer to "additives" and "counterion moieties" including "cyclodextrins", "zwitterionic surfactants", "polyols", "halide", "sulfate", "alkylfulfonate", and others. Support could not be found in the specification for the claimed subject matter.

8. Claim 44 recites onium polymers including "poly(vinylbenzylammonium salts)". Support could not be found in the specification for the recited compounds.

Claim Objections

3. Claims 1, 6-7, 9, 11, 27, 29-30, 40, and 44 are objected to because of the following informalities:

4. Claim 1 recites "detecting first and second chemiluminescent signals" at line 9. It is suggested that the claim recite "detecting **the** first and second chemiluminescent signals" in order to clarify that the signals are those previously referred to in lines 6-9 of the claim.

5. Claim 1 is a run-on sentence at lines 11-15 (the two "wherein" clauses that are separated by a comma).

6. Claims 6-7, 9, 11, 27, and 29 recite "the support surface". It is suggested that the claims refer to "the surface layer of the solid support" in order to maintain consistent terminology with that used in claim 1.

7. Claim 30 recites "the composition". It is suggested that the claim refer to "the substrate composition" in accordance with claim 1.

8. Claim 44 is objected to because it appears that in the compounds recited, the word "salts" should be placed outside of the parentheses.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-33 and 39-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections. See MPEP § 2172.01. The omitted structural cooperative relationships are: that the probes are **immobilized** on the surface layer of the solid support. The claim recites that a plurality of probes "disposed in" discrete areas on the surface layer of the solid support. The specification discloses that microarray technology involves that the probes be *immobilized* in discrete areas (p. 1, line 21). It would seem to be essential that the probes are immobilized in order to detect different signals in different discrete areas, since otherwise, the probes could be washed away upon application of the liquid substrate composition. It is suggested that the claim recite that the plurality of probes are "immobilized" "disposed in" the plurality of discrete areas.

12. Claims 1 is indefinite because it is unclear whether the solid support actually includes probes bound to the enzyme conjugates or not. The claim recites that at least some of the plurality of probes **are bound** to the enzyme conjugates, which suggests that the support is provided with probes that are already bound to the enzyme conjugates.

However, dependent claims 11-13 and 19-22 recite methods according to claim 1 in which the support is contacted with a sample that includes *target molecules labeled with the enzymes* (i.e., the enzyme conjugates are present in the sample). In these claims, the binding of the enzyme conjugates to the probes appears to be an active method step that occurs during the performance of the methods. For example, claim 11 recites "contacting the support surface" with a sample that includes the first and second enzyme conjugates (see claim 12), yet the support surface that is being referred to (that of claim 1) already has probes bound to enzyme conjugates disposed on the surface layer according to claim 1. It appears that the dependent claims recite method steps that occur before those of claim 1, but this is not clearly recited in the claims.

The claims are indefinite and confusing because it is unclear when the probes become bound to the enzyme conjugates, and in particular whether the probes/enzyme conjugates are actually bound to the solid support of claim 1.

13. Claim 4 recites the limitation "the amount" in line 1. There is insufficient antecedent basis for this limitation in the claim.

14. Claims 5 and 29 recite the limitation "the intensity". There is insufficient antecedent basis for this limitation in the claim.

15. Claims 6 and 9 recites the limitation "the location". There is insufficient antecedent basis for this limitation in the claims.

16. Claim 7 recites that control probes are located in one or more discrete areas on the support surface. The claim is indefinite because it depends from claim 3, which recites that the discrete areas comprise one or more control probes bound to the first enzyme conjugate. It is unclear whether the control probes recited in claim 7 are the same as those in claim 3.

17. Claim 19 recites the limitation "the plurality of **different** probes". There is insufficient antecedent basis for this limitation in the claims since claims 1, 11, and 18 from which claim 19 depends, do not refer to the plurality of probes as being "different".

18. Claims 20-21 are rejected as indefinite for the recitation of "nucleic acids derived from the mRNA transcripts" and "cDNA or cRNA derived from mRNA transcripts". The specification does not define how nucleic acids, cDNA, or RNA are "derived from" mRNA transcripts or indicate by what processes by which they may be so derived. In the absence of a specific definition for this term, the scope of the claim cannot be determined. Nucleic acids could be "derived from" mRNA transcripts by such diverse processes as transcription, mutation, subcloning, etc. The use of this terminology does not allow for the metes and bounds of the claims to be adequately identified.

19. Claim 29 recites the limitation "the emissions" in line 1. There is insufficient antecedent basis for this limitation in the claim.

20. Claim 29 recites the limitation "the combined signal". There is insufficient antecedent basis for this limitation in the claim.

21. Claims 41 and 42 recite the limitations "the corresponding target molecules" and "the corresponding enzyme conjugate", respectively. There is insufficient antecedent basis for these limitations in the claims.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 3-7, 9-26, and 28-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bronstein et al. (US 4,931,223) in view of Fodor et al. (US 6,309,822 B1).

Bronstein et al. teach a method of detecting chemiluminescent emissions on a solid support (coated matrix such as a nylon membrane), comprising contacting a surface layer of the solid support with a substrate composition that is a mixture of two or more enzymatically cleavable chemiluminescent substrates that are capable of being activated (cleaved) by different enzymes (see in particular the abstract; column 1, line 53 to column 3, line 3; column 7, lines 5-19; column 8, lines 1-21; Examples I-II; and claim 17 in particular). The signals produced by the two chemiluminescent substrates are then detected either simultaneously or sequentially (column

2, line 11; column 8, lines 16-21 and 42-65; column 11, lines 3-19). Bronstein et al. further teach that a plurality of probes may be immobilized in discrete areas ("spots") on the solid support (see column 8, lines 1-7; column 10, lines 29-36; column 11, lines 15-18; column 13, lines 5-18). The probes may be capture antibodies as in Example I or nucleic acid probes as in Example II (see also column 2, line 64 to column 3, line 3). At least some of the probes are bound to a first enzyme conjugate comprising the first enzyme, and at least some of the probes are bound to a second enzyme conjugate comprising the second enzyme (see the above passages and especially column 8, lines 1-21).

Bronstein et al. fail to specifically teach that the plurality of probes are immobilized in the discrete areas at a density of at least 50 discrete areas per cm2.

Fodor et al. teach high density probe arrays, in which greater than about 400,000 different probes can be immobilized per cm2 (see in particular the abstract; column 2, lines 33-43; column 3, lines 18-48). The high density probe arrays can be used to detect and quantify target nucleic acid sequences and/or to monitor the expression of a multiplicity of genes (column 33, lines 20-31; column 5, lines 34-36; column 2, lines 53-61). Fodor et al. teach that the high density probe arrays offer several advantages, including reduced intra- and inter-array variability, increased information content, and higher signal-to-noise ratio (see column 12 to column 15, line 60). In particular, Fodor et al. note that the arrays have advantages over blotted arrays (which is the technique used in Bronstein et al.), such as significantly higher hybridization efficiencies (column 14, line 61 to column 15, line 12).

Therefore, it would have been obvious to one of ordinary skill in the art to employ the high density probe arrays of Fodor et al. as the solid support in the method of detecting

chemiluminescent emissions of Bronstein et al. in order to allow for increased information content and massively parallel processing of hybridization data, reduction of assay variability, and/or to detect and quantify a multiplicity of genes with increased information content and sensitivity.

One would have a reasonable expectation of success in using the solid support of Fodor et al. in the method of detecting chemiluminescent emissions of Bronstein et al. because Fodor et al. teach that the microarrays may be used in methods employing chemiluminescent detection (column 49, lines 5-12, column 82, lines 43-65) and also that enzyme labels may be used (column 20, lines 51-61). One would also have a reasonable expectation of success because Fodor et al. teach that the solid support may be a nylon membrane (column 95, lines 49-57), which is the same material used as the solid support by Bronstein et al. One would also have a reasonable expectation of success because Bronstein et al. teach that the chemiluminescent detection method can be used in any art-recognized immunoassay, chemical assay, or nucleic acid probe assay technique (column 2, lines 54-68).

With respect to claims 3-7, Fodor et al. teach that in addition to test probes, the array can include control probes or normalization controls, which can serve to calculate a background signal and to allow for quantification of unknowns, or as expression level controls (column 14, lines 28-35; column 4, lines 6-12; column 9, lines 6-46; column 19, lines 14-21; column 22, line 57 to column 24, line 39; and column 35, line 29 to column 36, line 61). The control probes can be localized at any position in the array or at multiple positions throughout the array (column 23, lines 20-23). The intensity of the second (unknown) signal is quantified by comparing the signal intensity to that of mismatch control and/or background signal intensity (column 24, lines 9-15;

column 26, lines 10-25). The signals are detected by detecting the signal strength at each location (representing a different probe) on the array (column 35, lines 29-44).

With respect to claim 9, Bronstein et al. teach detecting the location of the signals on the solid support in that the brightness of the spots are visualized (see for example column 11, lines 15-19).

With respect to claim 10, Bronstein et al. teach nucleic acid probes (column 2, line 64 to column 3, line 3).

With respect to claims 11-12, Bronstein et al. teach contacting the solid support with a solution containing first target molecules labeled with the first enzyme (anti-beta-HCG antibodies conjugated to alkaline phosphatase) and second target molecules labeled with the second enzyme (anti-HLH antibodies conjugated to carboxylesterase) (Example I).

With respect to claim 13, Fodor et al. also teach samples comprising target nucleic acids, in which the targets may be labeled with enzymes (column 20, line 28 to column 21, line 24). Different targets may be labeled with different labels (column 81, lines 16-38). Fodor et al. teach that enzyme labels may be added to the target molecules prior to or after hybridizing with the immobilized probes--i.e., that the enzyme labels may be "direct" or "indirect" labels (column 20, line 51 to column 21, line 24). For example, Fodor et al. teach that target nucleic acids may be biotinylated, which allows them to be subsequently labeled with an avidin-conjugated label after the target nucleic acids are hybridized to the probes. As such, it would have been obvious to one of ordinary skill in the art to indirectly label the target molecules since Fodor et al. teach that both indirect and direct labeling are effective means of labeling target molecules.

With respect to claim 14, Fodor et al. teach that the target molecules may be pools of nucleic acids (column 2, line 62 to column 6, line 9). For example, the sample may comprise a first pool (total RNA pool) that is mixed or spiked with a second pool of 13 target RNAs (see column 103, line 45 to column 104, line 8). As another example, a sample including target pool of nucleic acids can be used together or "spiked" with a second pool of control nucleic acids (column 24, lines 22-39; column 9, lines 35-41; column 6, lines 36-63).

With respect to claims 15-16, Fodor et al. teach that the target nucleic acid sample may comprise mRNA transcripts or nucleic acids derived from mRNA transcripts, such as cDNA derived (reversed transcribed) from mRNA (column 17, line 47 to column 18, line 34; column 18, lines 35-54).

With respect to claim 17, Fodor et al. teach that the concentration of the target nucleic acids is proportional to the transcription level (and therefore expression level) of that gene (column 18, lines 9-34).

With respect to claims 18-22, Fodor et al. teach control probes as discussed above with respect to claim 3, and both Bronstein et al. and Fodor et al. each teach samples comprising target nucleic acids, in which the targets may be labeled with different enzymes as discussed above with respect to claims 11 and 13. The sample of Fodor et al. may include pools of nucleic acids that are mRNA transcripts or nucleic acids derived from mRNAs such as cDNA discussed above with respect to claim 14. Fodor et al. teach that the concentration of the target nucleic acids is proportional to the transcription level (and therefore expression level) of that gene as discussed above with respect to claim 17.

With respect to claims 23-26, Fodor et al. teach arrays with densities of 400,000 per cm2.

With respect to claims 28-29, Bronstein et al. teach that the first and second chemiluminescent substrates emit light of different wavelengths (see for example the abstract), and that the signals are imaged using multiple filters that isolate the different signals from each of the chemiluminescent substrates (column 13, lines 43-52; column 8, lines 16-21).

With respect to claims 30 and 32, Bronstein et al. teach that the composition comprising the two chemiluminescent substrates includes carbonate buffer (see column 10, lines 48-54) and further that the chemiluminescent substrates are both 1,2-dioxetanes (see for example the abstract).

With respect to claim 31, Bronstein et al. teach a wash step prior to addition of the substrate composition (column 10, line 59 to column 11, line 2; column 13, lines 36-39).

12. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bronstein et al. in view of Fodor et al. as applied to claim 6 above, and further in view of Ferea et al. (US 6,905,826).

Bronstein et al. and Fodor et al. are as discussed above, which teach control probes, but which fail to specifically teach that the control probes are located in one or more of the same discrete areas as probes for a target molecule.

Ferea et al. teach methods for detecting target molecules in a sample using microarrays, and in particular, controls to be used in such methods in order to allow for correction of irregularities in the shape, size, and intensity of microarray features (column 5, lines 49-52). Control signals can also be used to quantify the experimental signal (column 6, lines 16-19). Control oligonucleotide probes may be deposited onto the array in the same discrete areas

('features') as the experimental probes in order to serve as hybridization controls (column 6, lines 41-60; claim 1 and Figure 4 in particular).

Therefore, it would have been obvious to one of ordinary skill in the art to employ control probes located in the same discrete areas as the experimental probes as taught by Ferea et al. in the method of detecting chemiluminescent emissions of Bronstein et al. and Fodor et al. in order to act as an experimental control to determine whether hybridization is occurring. One would have a reasonable expectation of success because Ferea et al. relates to methods of detection based on nucleic acid hybridization using microarrays, which is the same format of Fodor et al.

13. Claims 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bronstein et al. in view of Fodor et al. as applied to claims 13-14 above, and further in view of Akhavan-Tafti et al. (US 6,068,979, Applicant's Information Disclosure Statement of 8/28/03).

Bronstein et al. and Fodor et al. are as discussed above, which teach samples comprising targets that may be pools of nucleic acids and that may be labeled with enzymes. Fodor et al. also teaches indirect labeling of the targets, for example by labeling of the targets with biotin (see especially column 1, lines 3-24). However, the references fail to specifically teach that the target molecules are indirectly labeled with *digoxigenin* or that the enzyme conjugates are *antidigoxigenin:enzyme* conjugates.

Akhavan-Tafti et al. teach binding pairs, including antigen-antibody and biotin-avidin or streptavidin interaction that may be used in labeling molecules with enzymes for chemiluminescent detection. One member of a binding pair may be attached to an enzyme in

order to form an enzyme conjugate, which is then capable of interacting with a target molecule labeled with the other member of the binding pair (column 4, lines 30-40 and column 5, lines 18-28). Specific examples of antigen-antibody binding pairs include antidigoxigenin-digoxigenin, where antidigoxigenin-enzyme conjugates are used as the enzyme conjugate (columns 15-16, Example 2, and Figure 3).

Therefore, it would have been obvious to one of ordinary skill in the art to indirectly label the target molecules with digoxigenin followed by labeling with an antidigoxigenin-enzyme conjugate as taught by Akhavan-Tafti et al. in the method of Bronstein et al. and Fodor et al. because Akhavan-Tafti et al. teach that both biotin-avidin (taught in Fodor et al.) and the digoxigenin-antidigoxigenin are binding pairs that can be used for indirectly labeling nucleic acids, which is the same purpose for which the biotin-avidin system is used in Fodor et al. It would have been further obvious to employ the digoxigenin-antidigoxigenin system of Akhavan-Tafti et al. in order to label the pool of target nucleic acids that are cDNA since cDNA is one type of nucleic acid sample that may be indirectly labeled and detected in Fodor et al. (see column 17, line 56 to column 18, line 8).

One would have a reasonable expectation of success because Fodor et al. teaches indirect labeling generically; although Fodor et al. provide the example of biotin-avidin, there is no indication that the indirect labeling is intended to be restricted to this binding pair. One would also have a reasonable expectation of success because both Akhavan-Tafti et al. and Fodor et al. teach indirect labeling of nucleic acids with labels that may be enzymes.

14. Claims 2, 39-40, and 44-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bronstein et al. in view of Fodor et al. as applied to claim 1 above, and further in view of Voyta et al. (US 5,145,772, Applicant's Information Disclosure Statement of 8/28/03).

Bronstein et al. and Fodor et al. are as discussed above, which teach a method of detecting chemiluminescent emissions on a solid support using a two-substrate composition, but which fail to specifically teach that the two-substrate composition is contacted with the solid support in the presence of a *composition comprising a chemiluminescent quantum yield enhancing material.*

Voyta et al. teach that enhancement agents such as BSA, polymeric quaternary onium (amm**onium**) salts (e.g. poly(vinyl-benzyltrimethylammonium) chloride, polyvinyl alcohol, and globular proteins act as enhancement agents in chemiluminescent assays by stabilizing light-emitting fluorophores, allowing for greater signal intensity (see the abstract; column 2, lines 45-64; column 5, line 17 to column 6, line 45; and Table I in particular). Voyta et al. teach that the enhancement agent may be simply added to the chemiluminescent substrate composition (column 13, lines 10-17), such that the chemiluminescent substrate composition would be contacted with the solid support in the presence of the enhancement agent. Other water soluble oligomeric, homopolymeric, and copolymeric materials can be used as enhancers in addition to or instead of quaternary ammonium polymers (column 5, line 65 to column 6, line 45). These include polyacids and salts thereof, polyvinyl alcohol, and synthetic polypeptides.

Therefore, it would have been obvious to include an enhancement agent such as a quaternary onium polymer at the same time the two-substrate composition is contacted with the sample (and therefore with the solid support) as taught by Voyta in the method of detecting

chemiluminescent emissions of Bronstein et al. and Fodor et al. in order to enhance the chemiluminescent signals.

With respect to claim 39, it would have been further obvious to include BSA as an additive because Voyta et al. teach that these compounds, like quaternary onium polymers, also serve to enhance the chemiluminescent signal. It would have been similarly obvious to further include polyvinyl alcohol (which is both an alcohol and a polyol) because Voyta et al. teach that this may be additionally used along with quaternary ammonium salts (see column 5, line 65 to column 6, line 23).

With respect to claim 40, Voyta et al. teach that the polymeric enhancer substances also include a counterion moiety such as halide, sulfate, arylsulfonate, alkylfulfonate, and combinations thereof (see in particular column 4, right column, the structure and line 64 to column 5, line 10).

With respect to claims 44-45, the compound poly(vinyl-benzyltrimethylammonium) chloride taught by Voyta et al. is an onium copolymer ("poly") as well as a poly(vinylbenzylammonium) salt.

15. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bronstein et al. in view of Fodor et al. as applied to claim 1 above, and further in view of Oldham et al. (US 6,970,240 B2).

Bronstein et al. and Fodor et al. are as discussed above, which teach a method of detecting chemiluminescent emissions on a solid support (microarray), but which fail to specifically teach that the support surface further comprises a fluorescent control.

Oldham et al. teaches an apparatus for imaging an array using fluorescent or chemiluminescent detection (column 1, lines 1-58). In particular, Oldham et al. teach that at least some of the discrete areas ("feature") of the solid support (sample tile 42) may include a fluorescent marker (see also column 2, lines 18-58). The fluorescent signals generated allow for auto-focusing of the array, to allow for the size and shape of each feature in the array to be easily determined, and to normalize the chemiluminescent signals (column 3, line 55 to column 4, line 32). A normalizing fluorescent image is first collected, followed by detection of chemiluminescent signals (column 7, line 20 to column 8, line 51).

Therefore, it would have been obvious to one of ordinary skill in the art to include a fluorescent marker in the microarray solid support of Fodor et al. in order to allow for normalization of chemiluminescent signals. One would have a reasonable expectation of success because Oldham et al. teach that the apparatus is intended to be used in detection methods using nucleic acid microarrays and chemiluminescent signals, which describes the method of Bronstein et al. and Fodor et al.

16. Claims 1, 9-10, 23-26, 28-29, and 32-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bers et al. (UK Patent Application GB 2 246 197 A, published 1/22/92) in view of Fodor et al.

Bers et al. teach a method of detecting chemiluminescent emissions on a solid support, where a plurality of probes ("macromolecular species" 12) are immobilized in a plurality of discrete areas (e.g. a "planar array", see claim 9) on a surface layer of the solid support, and where at least some of the probes are bound to a label 13 that may be an enzyme such as alkaline

phosphatase (see in particular the abstract; Figure 1; p. 3, line 32 to p. 4, line 35; p. 9, lines 1-3; p. 10, lines 7-18). The immobilized probes may comprise different types or groups that are each bound to distinct enzyme labels (see p. 3, line 32 to p. 4, line 11 and claims 3 and 7 in particular). Chemiluminescent emissions are detected by contacting the solid support with a mixture of a plurality of chemiluminescent substrates, where each substrate is activated ("induced") by one of the distinct enzyme labels to undergo chemiluminescent reaction (ibid and p. 7, lines 3-9). The signals are then detected using a phosphor screen. The solid support 11 may be a nitrocellulose or nylon membrane, coated glass, or a plastic microtiter plate (p. 8, lines 20-24).

Bers et al. fail to specifically teach that the probes are immobilized in discrete areas *at a density of at least 50 discrete areas per cm2.*

Fodor et al. (as discussed above) teach high density probe arrays, in which greater than about 400,000 different probes can be immobilized per cm2 (see in particular the abstract; column 2, lines 33-43; column 3, lines 18-48). The high density probe arrays can be used to detect and quantify target nucleic acid sequences and/or to monitor the expression of a multiplicity of genes (column 5, lines 34-36; column 2, lines 53-61). Fodor et al. teach that the high density probe arrays offer several advantages, including reduced intra- and inter-array variability, increased information content, and higher signal-to-noise ratio (see column 12 to column 15, line 60). In particular, Fodor et al. note that the arrays have advantages over blotted arrays (which is the technique used in the Example of Bers et al.), such as significantly higher hybridization efficiencies (column 14, line 61 to column 15, line 12).

Therefore, it would have been obvious to one of ordinary skill in the art to employ the high density probe arrays of Fodor et al. as the solid support in the method of detecting

chemiluminescent emissions of Bers et al. in order to allow for massively parallel processing of hybridizations, and/or to detect and quantify a multiplicity of genes with increased information content and sensitivity.

One would have a reasonable expectation of success in using the solid support of Fodor et al. in the method of detecting chemiluminescent emissions of Bers et al. because Fodor et al. teach that the microarrays may be used in methods employing chemiluminescent detection (column 49, lines 5-12, column 82, lines 43-65)) and also that enzyme labels may be used (column 20, lines 51-61). One would also have a reasonable expectation of success because Fodor et al. teach that the solid support may be a nylon membrane (column 95, lines 49-57), which is an example of material taught by Bers et al. One would also have a reasonable expectation of success because Bers et al. teach that the chemiluminescent detection method can be applied to a wide range of assays (p. 19, lines 32-36).

With respect to claim 9, Bers et al. teach that the detection procedure provides localized information and can be used to image spatial arrays of macromolecules (p. 8, lines 7-12).

With respect to claim 10, the probes may be nucleic acid molecules (the abstract; p. 8, line 34 to p. 9, line 3; p. 7, lines 20-22).

With respect to claims 23-26, Fodor et al. teach arrays with densities of 400,000 per cm2.

With respect to claims 28-29, Bers et al. teach that two chemiluminescent substrates may be used that have different emission maxima (p. 6, lines 30 to p. 7, line 2) and that that filters may be used in order to discriminate the different signals (p. 7, lines 3-16).

With respect to claims 32-33, Bers et al. teach that 1,2-dioxetanes and/or luminol may be used as chemiluminescent substrates in the mixture, and also that any known chemiluminescent reaction may be utilized (p. 4, lines 12-31; p. 6, lines 30-36).

Double Patenting

22. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

23. Claims 1-33 and 39-45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3-10, 13-19, and 21-45 of copending Application No. 10/620,332 in view of Bronstein et al.

Although the conflicting claims are not identical, copending Application No. 10/620,332 also claims a method of detecting chemiluminescent emissions on a solid support, including the steps of contacting a surface layer of the solid support with first and second substrate

compositions comprising a first and second chemiluminescent substrate, respectively, that is capable of being activated by first and second enzymes to produce a first and second chemiluminescent signals (see claim 1). Application No. 10/620,332 further teaches detecting the first and second chemiluminescent signals on the surface layer of the solid support, wherein a plurality of probes are located in a plurality of discrete areas on the surface layer at a density of at least 50 discrete areas per cm2, and wherein at least some of the probes are bound to a first enzyme conjugate comprising the first enzyme, and at least some of the probes are bound to a second enzyme conjugate comprising the second enzyme. Dependent claims also recite that the first and second target molecules may be pools of nucleic acids (see claims 16-19 and 45).

Application No. 10/620,332 differs in that the two chemiluminescent substrates are contacted with the solid support separately and detected sequentially. The reference therefore fails to specifically teach that a composition comprising both substrates is contacted with the solid support.

However, Bronstein et al. teach a method for detecting chemiluminescent emissions in which two chemiluminescent substrates are employed, which are provided together in a single composition and then applied to a solid support (nylon membrane) (see column 1, line 53 to column 2, line 19; and Examples 1-2). Therefore, it would have been obvious to one of ordinary skill in the art to apply the substrates together as a mixture, as taught by Bronstein et al., in order to reduce the number of operational steps. One would have a reasonable expectation of success because Bronstein et al. teach that the two-substrate mixture can be used with either simultaneous or sequential detection of chemiluminescent signals (see column 2, line 11 in particular).

Note that with regard to the detection steps, the instant application is generic to Application No. 10/620,332 in that independent claim 1 recites detecting first and second chemiluminescent signals, but does not recite a particular order in which the signals are detected. This fully encompasses the method recited in claim 1 of Application No. 10/620,332, which includes the limitation that the signals are detected sequentially; the first composition is applied and detected, and then the second composition is applied and detected. In contrast, the instant application does not require a particular order in which the first and second signals are detected. Application No. 10/620,332 therefore represents a species that anticipates the genus of detecting first and second signals as recited in the instant application.

24. Claims 1-33 and 39-45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28-47 of copending Application No. 10/462,742 in view of Akhavan-Tafti (US 6,068,979) and Bronstein et al.

Although the conflicting claims are not identical, Application No. 10/462,742 also claims a method of detecting chemiluminescent emissions on a solid support, including the steps of contacting a surface layer of the solid support with a composition comprising a chemiluminescent substrate capable of being cleaved by an enzyme to produce chemiluminescence; and detecting chemiluminescent emissions on the solid support (claim 28). Application No. 10/462,742 further recites that a plurality of probes are disposed in a plurality of discrete areas on the surface layer at a density of at least 50 discrete areas per cm2. At least some of the probes are bound to an enzyme conjugate comprising an enzyme capable of cleaving the chemiluminescent substrate (claim 28)

Application No. 10/462,742 fails to recite a method in which the solid support is contacted with a *second substrate composition* capable of being cleaved by a *second enzyme* that is provided as a *second enzyme conjugate* bound to some of the probes on the solid support, and in which both these first and second chemiluminescent signals are detected.

However, Akhavan-Tafti et al. teach a method of detecting chemiluminescent emissions on a solid support using two chemiluminescent substrates paired with two different enzymes capable of activating the two substrates, in which signals are detected from both the first and second substrates on the support (see in particular the abstract; column 1, lines 55-59; column 2, lines 38-64). Akhavan-Tafti et al. teach that using multiple substrates and multiple enzymes allows for multiple analytes in a sample to be detected in a single assay on the same support (blot). Bronstein et al. teach that in methods employing multiple chemiluminescent substrates for detection of multiple targets, the substrates may be combined as a mixture and added together (see Examples 1-2 in particular).

Therefore, it would have been obvious to one of ordinary skill in the art to include a second chemiluminescent substrate capable of being cleaved by a second enzyme and to detect the signal from this second substrate in the method of Application No. 10/462,742 because Akhavan-Tafti et al. teach that application and detection of multiple chemiluminescent reagents to a single support allows for detection of multiple analytes in a sample. It would have been further obvious to provide the two substrates as a mixture as taught by Bronstein et al. for simplicity and to reduce the number of operational steps.

The above are provisional obviousness-type double patenting rejections.

Conclusion

17. No claims are allowed.

18. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Bronstein et al. (US 5,654,154) is also cited for relevance to claims 2 and 39 for its teaching of additives such as cationic, anionic, zwitterionic or neutral surfactants, negatively charged salts, and alcohols (see in particular column 3, lines 20-46; and column 10, lines 25-42).

Tonkinson et al. ("Chemiluminescent Detection of Immobilized Nucleic Acids--From Southern Blots to Microarrays"; In: Luminescence Biotechnology: Instruments and Applications, Edited by Van Dyke et al., CRC Press: Boca Raton, FL, 2002) is cited for its teaching of chemiluminescent detection of nucleic acids on solid supports such as microarrays. Tonkinson et al. also teach direct and indirect labeling strategies, including the digoxigenin-antidigoxigenin system (see p. 193).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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